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<input type="checkbox"/> Additional Inventors are being named on the <u>0</u> separately numbered sheets attached hereto.					
TITLE OF THE INVENTION (280 characters max)					
METHOD AND APPARATUS FOR ARCHIVING BIOLOGICAL SAMPLES IN A SOLID STATE MANNER					
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ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification	Number of Pages	5	<input checked="" type="checkbox"/> Small Entity Statement		
<input checked="" type="checkbox"/> Drawing(s)	Number of Sheets	1	<input type="checkbox"/> Other (specify)	postcard	
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Respectfully submitted,

Diane L. Gardner
Signature

Name Diane L. Gardner, Reg. No. 36,518Date October 28, 1999Telephone No. (858) 678-4355Docket No. 07762-008001

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Attorney's Docket No.: 07762-008001

PROVISIONAL APPLICATION FOR PATENT

under

37 CFR §1.53(c)

60151594.102599

TITLE: METHOD AND APPARATUS FOR ARCHIVING
BIOLOGICAL SAMPLES IN A SOLID STATE MANNER

APPLICANT: STAFFORD BRIGNAC

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Name of Small Business Concern: GENOMETRIX INCORPORATED
Address of Small Business Concern: 3608 Research Forest Drive, Suite B7
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hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled **METHOD AND APPARATUS FOR ARCHIVING BIOLOGICAL SAMPLES IN A SOLID STATE MANNER** by inventor(s) **MICHAEL B. HOGAN** described in:

- ☒ the specification filed herewith.
☐ application serial no. __ filed __.
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100% (100%)

Date: 10/26/95

**METHOD AND APPARATUS FOR PUNCHING A PELLET FROM A SUBSTRATE
CONTAINING A SAMPLE**

BACKGROUND

The related fields of pharmacogenomics and genetic
5 epidemiology have matured rapidly as spin-offs from the human
genome project. Single nucleotide polymorphism (SNP) data is
accumulating at a rapid pace due to re-sequencing of the human
genome. Large-scale SNP discovery initiatives in the U.S. and
Japan are defining high variability in the genetic make-up of
10 the human population at the nucleotide level.

Such large-scale genetic projects require the study of
gene polymorphism in very large human sample sets, as large as
100,000 to 500,000, in a manner that allows rapid, random
access to genetic material from such samples at rates on the
15 order of thousands per day.

As a result of managing such large sample libraries, a
bottleneck has developed relative to the long-term storage of
DNA samples and rapid, random-access retrieval of DNA from
such libraries. It is therefore desirable to provide
20 technology supporting high-throughput genotyping that includes
the permanent storage and indexing of such samples and rapid,
addressable and substantially automatic processing of the
genetic material in such samples.

SUMMARY

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description
5 below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 is a perspective view of a punching system
10 according to an embodiment.

FIG. 2 is a plan view of a slide according to an embodiment.

FIG. 3 is a top perspective view of the embodiment of FIG. 1.

15 FIG. 4 is another perspective view of the embodiment of FIG. 1.

FIG. 5 is a cross-sectional view of a punch head according to an embodiment.

FIG. 6 is a block diagram of a position controller
20 according to an embodiment.

FIG. 7 is a block diagram of a punching controller according to an embodiment.

Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

FIG. 1 illustrates an embodiment of a sample punching apparatus 10 provided for selecting a slide 12 stored in a storage container 18 that includes a flexible substrate 14 having a genetic sample attached thereto, punching a pellet 80 from the flexible substrate, depositing the pellet in a well 60 of a multiwell tray 62, and returning the slide to the storage container.

According to the present embodiment, the slide 12 includes a flexible substrate 14 on which a biological sample has been deposited, as shown in FIG. 2. The flexible substrate is contained in a relatively rigid frame 16. A number of such slides are stored in a rack 18 (FIG. 7). An indexing motor 20 indexes the rack 18 to a position corresponding to a selected slide. The rack 18 has an opening 22 in the back exposing the rear sides of the slides, as shown in FIG. 3. A feed tongue 24 ejects the selected slide from the rack. The feed tongue 24 pushes the slide through a feed slot in a separating plate 26 and onto a punching pad 36.

FIG. 4 illustrates an arm 28 with a platform 30 including a punch head 32. The arm 28 is mounted on an x-y-z stage 34.

A position controller 100 (see FIG. 6) controls the stage to different positions in the x-y-z space. The position controller 100 moves the punch head 32 over the flexible substrate 14 resting on the punching pad 36. Arm 28 is
5 mounted on vertical brackets 38 and is controlled to descend vertically (i.e., in the z-axis) causing the punch head to punch a pellet 80 containing genetic material from the flexible substrate 14 (see FIG. 2). A pneumatic press 40 may be used to actuate the arm 28 for punching the pellet 80.

10 FIG. 5 illustrates a cross-section of the punch head 32. Punch head 32 includes a tip 42 with a pellet-retaining reservoir 44. The reservoir 44 extends into a bore 48. A piston 46 is housed in the bore with one end 47 closely fit to the bore size of the reservoir. The tight fit provides a
15 cleaning action in the reservoir when a pellet is ejected. This cleaning action substantially removes residual biological material, e.g., paper shreds, in the reservoir remaining from prior punching operations.

20 With the pellet 80 retained in the reservoir, the position controller 100 moves the arm 28 with tip 42 to a multiwell tray area and over a selected well 60 in multiwell tray 62. A solenoid 50 controlled rod 52 depresses the piston 46 through the bore, causing the punch head 32 to eject the

pellet 80 into the selected well 60 for subsequent liquid processing.

According to the present embodiment, during the above-described pellet depositing operation, the punched slide 12 is
5 returned to its original position in the rack 18 by a loading tongue 64 positioned in front of the punching pad 36 which pushes the slide back through the feed slot in the separating plate 26 and into its original position on the storage rack 18. Pneumatic presses may be used to actuate the feed tongue
10 24 and loading tongue 64.

FIG. 2 illustrates a sample slide 12 according to an embodiment. The flexible substrate 14 may be a paper material such as FTA paper manufactured by Fitzco. Other suitable papers are manufactured by Life Technologies, Inc. and other
15 suppliers.

The flexible substrate 14 is held in relatively rigid frame 16. The frame 16 may have the dimensions of slides typically used for 35 mm photographic slides. The material for the frames may be, for example, cardboard or plastic.

20 The slide 12 may have indexing indicia 70 printed, stamped, or otherwise placed thereon. The indexing indicia 70 may be, for example, alphanumeric characters or a bar code for identification by an OCR or bar code scanner, respectively, or other machine reader 72 in the apparatus 10.

The paper substrate 14 accepts a blot of blood or other biological sample material. Once the biological sample is deposited on the paper, the cells lyse and component DNA adheres to the paper. Preferably the DNA sticks to the paper substrate 14 firmly enough so that contaminants may be removed from the paper with hot water or detergent washing without contaminating or diluting the DNA sample. Examples of sample material include whole blood, blood serum, blood plasma, blood lymphocytes, fixed or unfixed tissue extracts, buccal scrapes, DNA, RNA, or protein. The paper substrate 14 may be impregnated with agents to inhibit the growth of mold or bacteria during long periods of storage at approximately normal (room) temperate and humidity.

The flexible substrate 14 may be sized to provide a number of pellets 80. According to an embodiment, the pellets 80 may be between about 1 and 3 mm in diameter. According to the present embodiment, the slide may be punched up to 96 times to provide up to 96 circular pellets 80. The slide may be archived in the sample library between each punching operation. The pellets may be differently shaped or sized, depending on the shape of the tip 42 of the punch head 32.

Storage rack 18 (see FIG. 1) has a number of slots adapted to hold a number of slides. Slot positions in the rack may be marked to aid indexing. According to the present

embodiment, the storage rack is loaded in the apparatus 10 in a horizontal position, and then rotated by a horizontal-vertical actuator to a vertical position in which the rack butts up against separating plate 26.

5 Indexing motor 20 moves the storage rack 18 up and down to position the rack such that the selected slide 12 is aligned with the feed tongue 24. Indexing may be determined by the position of the rack and/or by machine reading of the indexing indicia on the slide by machine reader 72.

10 The punching pad 36 (see FIG. 3) may be constructed of a shock absorbing and "self-healing" material. Suitable materials include various hard plastics such as, for example, Delran or polyurethane.

 The arm 28 is controlled in the x, y directions by
15 position controller 100. As shown in FIG. 6, position controller 100 includes a microprocessor 102 having a memory 104 that includes data corresponding to the x, y coordinates of the punching area and of drop points for individual wells 60 in the tray area. Multiwell trays 64 come in various
20 sizes, such as 96-well, 384-well and 1536-well, all of which are encompassed by various embodiments.

 As described above, the flexible substrate 14 may be sized to provide a number of pellets 80. To avoid the same area of the flexible substrate 14 from being punched

repeatedly, in whole or part, and consequently fail to yield an adequate sample, a punching controller 150 may be provided. As shown in FIG. 7, punching controller 150 includes a microprocessor 152, which in one embodiment, is connected to a machine vision device 154, e.g., a digital camera, that is positioned over the slide 12 on the punching pad 36 to detect previously punched areas and determine viable punching areas on the paper substrate 14. According to an alternate embodiment, microprocessor 152 is connected to a slide database 156. Each indexed slide has an associated number of punching positions, each having an x, y coordinate stored in the database. The number and position of used and/or viable punching areas on each slide are stored in the database 156. Prior to punching, the indexing indicia 70 are read from the selected slide by reader 72. The position of a suitable punching area for that slide is determined from historical information for the selected slide 12 in the database 156. Position controller 100 controls punch head 32 to a position over the suitable punching area. Punching areas may be arranged in a virtual grid, each punching area having an associated number and/or x, y coordinate in the grid.

A sample punching apparatus according to an embodiment is contemplated for use in a PCR reaction assembly with a throughput capacity from 1,000 samples a day or greater.

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments
5 are within the scope of the following claims.

WHAT IS CLAIMED IS:

1 1. Apparatus comprising:

2 a feeder adapted to remove a selected substrate from a
3 storage container;

4 a movable arm;

5 a punch head mounted on the movable arm and comprising

6 a tip adapted to punch a pellet from the substrate,

7 a reservoir adapted to retain the pellet, said

8 reservoir adjacent the tip,

9 an ejector adapted to eject the pellet from the

10 reservoir; and

11 a position controller adapted to move the arm and

12 position the tip over the substrate in a first position

13 and position the tip over a sample container in a second

14 position, said ejector adapted to eject said pellet in

15 said second position.

1 2. The apparatus of claim 1, wherein the punch head

2 comprises a bore opening into the reservoir, and

3 wherein the ejector comprises a piston extending through

4 said bore, said piston adapted to push the pellet out of the

5 reservoir when actuated.

1 3. The apparatus of claim 2, wherein the piston has a
2 first end nearest the reservoir and a second end furthest from
3 the reservoir, the apparatus further comprising:
4 a rod contacting the second end of the piston; and
5 a solenoid connected to the rod and adapted to actuate
6 the rod.

1 4. The apparatus of claim 1, wherein the substrate
2 comprises a flexible substrate held in a frame.

1 5. The apparatus of claim 4, wherein the flexible
2 substrate comprises FTA paper.

1 6. The apparatus of claim 4, wherein the frame
2 comprises a 35 mm slide frame.

1 7. The apparatus of claim 1, wherein the storage
2 container comprises a plurality of slots, each adapted to hold
3 a substrate.

1 8. The apparatus of claim 1 further comprising a loader
2 adapted to return the substrate to an original position in the
3 storage container after the substrate is punched.

1 9. The apparatus of claim 1, wherein the sample
2 container comprises a well in a multiwell tray.

1 10. The apparatus of claim 1, wherein the substrate
2 comprises indexing indicia, said apparatus further comprising
3 a reader adapted to recognize the indexing indicia.

1 11. The apparatus of claim 10, wherein the indexing
2 indicia comprises a bar code, and wherein the reader comprises
3 a bar code reader.

1 12. The apparatus of claim 1 further comprising an
2 imaging device vision adapted to recognize previously punched
3 areas on the substrate, wherein the position controller is
4 connected to the imaging device and adapted to position the
5 tip over an unpunched area on the substrate in the second
6 position.

1 13. The apparatus of claim 12, wherein the imaging
2 device is a camera.

1 14. The apparatus of claim 10 further comprising a
2 database comprising data representative of punched or
3 unpunched areas on a substrate corresponding to a particular
4 indexing indicia, wherein the position controller is connected
5 to the database and is adapted to position the tip over an
6 unpunched region on the substrate in the second position.

1 15. Apparatus comprising:

2 a punching pad;
3 means for feeding a substrate from a substrate holder to
4 a punching pad;
5 a punch head comprising
6 a tip adapted to punch a pellet from the substrate,
7 a reservoir adapted to retain the pellet, said
8 reservoir adjacent the tip, and
9 means for ejecting the pellet from the reservoir;
10 means for positioning the tip over the substrate in a
11 first position; and
12 means for positioning the tip over a sample container in
13 a second position, said ejecting means ejecting said pellet in
14 said second position.

1 16. The apparatus of claim 15 further comprising means
2 for returning the substrate to an original position in the
3 substrate container after the substrate is punched.

1 17. The apparatus of claim 15, wherein the substrate
2 comprises a flexible substrate held in a frame.

1 18. The apparatus of claim 15, wherein the substrate
2 comprises indexing indicia, and further comprising means for
3 recognizing said indexing indicia.

1 19. The apparatus of claim 18 further comprising means
2 for identifying a viable punching area on the substrate, and
3 wherein the positioning means is connected to the identifying
4 means and is adapted to position the tip over the viable
5 punching area in the second position.

1 20. A method comprising:
2 removing a first substrate from a substrate holder;
3 positioning the first substrate over a punching pad;
4 punching a pellet from the first substrate with the tip
5 of a punch head and retaining the pellet in a reservoir in the
6 punch head;
7 moving the tip over a sample holder; and
8 depositing the tip in the sample holder.

1 21. The method of claim 20 further comprising:
2 loading the first substrate in the substrate holder after
3 the substrate is punched;
4 removing a second substrate from the substrate holder;
5 positioning the second substrate on the punching pad; and
6 moving the tip over the second substrate.

1 22. The method of claim 20, wherein the flexible
2 substrate comprises a flexible substrate held in a frame.

1 23. The method of claim 20, wherein the substrate
2 comprises indexing indicia, and further comprising recognizing
3 said indexing indicia.

1 24. The method of claim 20 further comprising:
2 identifying a viable punching area on the substrate; and
3 positioning the tip over the viable punching area in the
4 second position.

ABSTRACT

An automated punching system for paper substrates containing DNA samples. The paper substrates are held in slide frames and are loaded in a rack. A feeder removes a selected slide from the rack and positions it over a punching pad. A punch head with a circular tip punches a pellet from the paper substrate and retains it in a reservoir adjacent the tip. The punch head is connected to a movable arm which positions the tip over a desired well in a multiwell tray. The pellet is ejected by a solenoid actuated rod which presses a piston that extends into the reservoir. The pellet is deposited in the well for liquid processing. The punched slide is returned to the rack and a new slide is positioned on the punching pad.